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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,209	06/20/2003	Harry R. Howard	PC9953D	7318

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,209	HOWARD, HARRY R.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 6/20/03. There are fourteen claims pending and fourteen under consideration. Claims 1-6 are compound claims. Claims 8, 9, 12, and 13 are composition claims. Claims 10, 11, 14, and 15 are method of using claims. This is the first action on the merits. The application concerns some piperidine compounds, compositions, and uses thereof.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims none, drawn to piperazines of group G_1 and some of G^5 where R^6 and R^7 are an ethylene group, classified in class 544, subclasses 295, 364, 368, 372, and 379.

II. Claims none, drawn to piperidine compounds of group G^2, some of G^3 where p = 2, some of G^4 where p = 2, and some of G^6 where p = 2, classified in class 546, subclasses 208, 212, 213, and 214.

III. Claims none, drawn to bicyclopyrrolidine compounds of group G^3 where R^6 and R^7 are an ethylene group, classified in class 544, subclass 349.

IV. Claims none drawn to pyrrolidine compounds some of G^3 where p = 1, some of G^4 where p = 1, and some of G^6 where p = 1, classified in class 548, subclasses 517, 518, and 527.

V. Claims none, drawn to ethylenediamine compounds of group G^5, where R^6 and R^7 do not form a ring, classified in class 549, subclasses 72, 487, 537, and 548.

VI. Claims none, drawn to homopiperidine compounds of group some of G^3 where p = 3, some of G^4 where p = 3, and some of G^6 where p = 3, classified in class 540, subclasses 596 and 602.

Claims 1-6 and 8-15 link groups I-VI.

3. The inventions are distinct, each from the other because of the following reasons: the heterocyclic cores of these distinct inventions are the mandatory group R^1, represented by figures G^1 through G^6. These six different heterocycles have acquired a separate status in the art as shown by their different classification. The search required for Group I is not required for Group II-VI, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with David Joran on 1-12-05 a provisional election was made with traverse to prosecute the invention of Group II, parts of

claims 1-6 and 8-15. Applicant in replying to this Office action must make affirmation of this election.

5. Objection is made to claims 1-6 and 8-15 as containing non-elected subject matter. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. The claimed compounds, compositions, and methods that employ them present a variable core. Formula (I) contains compounds drawn to the non-elected inventions.

Priority

6. The specification needs to be amended. The status of non-provisional parent applications should also be included. Since the parent application has become a patent, please update the first line of the specification with the expression "now Patent No. 6,602,874" following the filing date of the parent application.

Title

7. The title of the invention is no longer descriptive after restriction. A new title is required that is clearly indicative of the invention to which the claims are directed. The examiner suggests adding the word "Piperidinyl" to the beginning of the title.

Claim Objections

8. Claims 9, 12, and 13 are objected to under 37 CFR 1.75 as being a duplicate of claim 8. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording,

it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The language in each of these four claims, "for treating .... in a mammal" is merely a statement of intent. It is a mental step with no physical consequences. Thus, each of these four claims is a composition of compounds of claim 1, and hence the four claims are identical.

9. Claims 14 and 15 are objected to under 37 CFR 1.75 as being a duplicate of claims 10 and 11 respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 14 and 15 amount to the same thing as claims 10 and 11, namely treatment of a disease in the same manner.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 11, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in

determining which are the "disorder or condition that can be treated or prevented by enhancing serotoninergic neurotransmission". It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a serotonin receptor enhaner and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The words "preventing" and "prevention" occur in lines 8, 16, 17, 19, 20, 21, 30, 31, and 34 of page 32 and lines 7, 8, 11, 19, 21, and 22 of page 33. Applicants are not enabled for preventing any diseases. The only established prophylactics are vaccines not the piperidine compounds such as present here. In addition, it is presumed that "prevention" of

the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before disease symptoms occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 38, page 14 to line 14, page 15 records the impressive list of diseases Applicants intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical psychiatric medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become depressed or

anxious before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in psychiatric diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of affective diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent affective disorders generally. That is, the skill is so low that no compound effective generally against affective disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula (I).

The Examiner suggests deletion of the word "prevention".

12. Claims 8-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating generalized anxiety disorders and migraine, does not reasonably provide enablement for treating the other listed diseases or treating every "disorder or condition that can be treated or prevented by enhancing serotoninergic neurotransmission". The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection were summarized above. The five main issues are the lack of any correlation between clinical efficacy for disease treatment and Applicants' two prophetic *in vitro* assays, the lack of any working examples of any compounds drawn to the present scope of claims, the total lack of any biological data on any compounds, the state of the prior art, and the breadth of the claims.

There is an *in vitro* assay, drawn to binding to the 5-HT_{1A} receptor, described in lines 8-29, page 16 with no data. Applicants do not state and it is not recognized in the psychiatric arts this assay is correlated to clinical efficacy for the treatment of any diseases. There is an *in vitro* assay, drawn to binding to the 5-

HT_{1D} receptor, described in the passage spanning line 20, page 15 to line 7, page 16, again with no data. Applicants do not state and it is not recognized in the psychiatric arts this assay is correlated to clinical efficacy for the treatment of any diseases. As discussed in the following enablement rejection there is no working example of a piperidine compound of the present claims ever being made, let alone tested.

The state of the clinical arts in 5-HT_{1A} receptor related diseases is provided by Gaster (Ann. Reports Med. Chem.) who states in the first complete paragraph on page 22 that no clinical utility of 5-HT_{1A} receptor antagonists is known. In the second complete paragraph on page 21 Gaster (Ann. Reports Med. Chem.) states that the drug buspirone, which as utility as an axiolytic agent, is an agonist at both pre- and post-synaptic 5-HT_{1A} receptor sites. The state of the clinical arts in 5-HT_{1D} receptor related diseases is provided by Robichaud (Ann. Reports Med. Chem.). Agonists of the HT_{1D} receptor are discussed in the final paragraph, page 12. The only disease associated with these agonists is migraine.

The scope of the claims involves all of the million of compounds of claim 1, the 29 specifically named diseases of claims 8, 10, 12, and 14, as well as the unknown list of diseases embraced by the phrase "disorder or condition that can be

treated or prevented by enhancing serotoninergic neurotransmission". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

13. Claims 1-6 and 8-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for using the piperidine compounds of the present claims. The specification is not adequately enabled for the scope of fused rings that have piperidine rings as radical R^1. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. The three main factors leading to this conclusion are the absence of any working examples with a piperidine ring at R^1, the differing physical and chemical properties between the

piperazine compounds actually made and the piperidine compounds presently claimed, and the unpredictability of physiological action.

a) Determining if any particular claimed compounds with a piperidine ring in R^1 would be active would require synthesis of the compound and subjecting it to testing with Applicants' two prophetic *in vitro* assays. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed piperidine compounds is found in line 18, page 2 to line 19, page 3, which merely states Applicants intent to make and use such compounds. c) In the instant case none of the working examples contains any Compounds where R^1 is the elected groups G^2-G^4 or G^6. All of the working examples correspond to Applicants formula G^1, which was the subject matter of the grandparent application. None of these working examples contain a non-basic carbon atom attached directly to the aromatic ring found in Y as in radical G^2. None of these working examples contain a two-atom linker to the heterocyclic ring and is radicals G^3 and G^4. None of the working examples contain a non-basic carbon atom at position 4 as in radical G^6. d) The nature of the invention is binding to the and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of both the 5-HT_{1A} receptor and the 5-HT_{1D} receptor, the binding

activity of small ligands to both receptors, and the ability of those compounds to inhibit neurotransmission. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) The state of the art is detailed knowledge of the both the 5-HT_{1A} receptor and the 5-HT_{1D} receptor is lacking. No X-ray structures of the receptors are known and the structural requirements of ligands to this receptor are poorly understood. The six-membered piperazine ring of Applicants' working examples is highly basic. The piperidine ring of the rejected compounds is moderately basic because it is directly attached to a benzene ring. The piperidine ring of the rejected compounds lacks the second hydrogen bond acceptors site of the working examples. The piperidine ring of the rejected compounds lacks a second nucleophilic and polarizable nitrogen atom of the piperazine of Applicants working examples. There is no reasonable basis for the assumption that the myriad of compounds embraced the present formula (I) will all share the same biological properties. The piperidine rings are chemically non-equivalent and there is no

basis in the prior art for assuming in the non-predictable art of 5-HT_{1A} receptor and the 5-HT_{1D} receptor pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724.

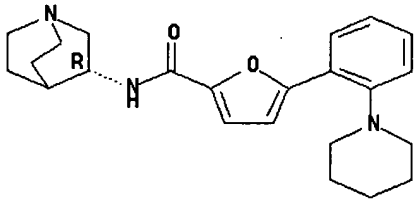
f) The artisan using Applicants invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such different rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to

make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

14. Applicants' compounds are novel over those of Myers ('385). The reference teaches compounds such as that shown below. However this is not a competent reference against Applicants claims both because of the effective priority date of the reference and because the azabicyclo[2.2.2]oct-3-yl radical does not Applicants limitations for R^3.



Conclusion

15. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

16. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624

TCMcK/me